REMARKS

Claims 1-19 are currently pending and under active consideration in this application. Claims 1-7 have been amended to delete the recitation "tautomer" and to recite a "physiologically acceptable" salt. Support for the recitation of "physiologically acceptable" salt of claims 1-7 can be found throughout the specification, *inter alia*, at page 17, paragraph 1. Claim 1 has been amended to delete the recitation wherein R_b is a diethylamino group. Claims 17-19 are currently amended to recite methods of preventing or treating "benign or malignant tumors and diseases of the airways and lungs" in a patient in need thereof. Support for the subject matter of claims 17-19 can be found throughout the specification and the claims as originally filed.

No new matter has been added.

Section 112 Rejections, Second Paragraph

Claims 1-19 are rejected under 35 USC §112, second paragraph as being indefinite.

The Examiner alleges that claims 1-7 are indefinite in the recitation of "tautomer". In response Applicants have deleted the recitation of "tautomer" from claims 1-7, thereby making this rejection moot.

The Examiner alleges that claims 1-7 are indefinite in the recitation of "salt thereof". Applicants disagree, however, claims 1-7 have been amended to recite "physiologically acceptable" salt, thereby overcoming this rejection.

The Examiner alleges that claims 8-10 recite "physiologically acceptable salt" which is not recited in the claims upon which they depend. Claims 1-7, as presently amended, recite "physiologically acceptable salt", thus this rejection is overcome.

The Examiner contends that claims 11-19 are rejected as being dependent on any one of claims 1-7, and carry on their limitations. Applicants submit that the rejections of claims 1-7 have been overcome, thereby making this rejection of claims 11-19 moot.

Applicants respectfully submit that, in view of the amendments and remarks above, the rejections under Section 112, first paragraph, have been overcome and must be withdrawn.

Section 112 Rejections, First Paragraph

Claims 17-19 are rejected under 35 USC §112, first paragraph for lack of enablement. The Examiner contends that Applicants' specification while being enabling for the treatment of benign tumors that are linked to the activity of EGF-R kinase, does not reasonably provide enablement for the treatments of other diseases such as: malignant tumors, airways and lungs, GI tract, bile duct, gall bladder.

Applicants disagree with this rejection for the reasons discussed below. Claims 17-19, as amended, are directed to methods of treating or preventing benign or malignant tumors and diseases of the airways and lungs.

Applicants direct the Examiner's attention to page 19 of the specification wherein it is shown that the compounds of general formula I according to the invention inhibit signal transduction by tyrosine kinases, as demonstrated by the example of the human epidermal growth factor receptor (EGF-R).

Applicants also direct the Examiner's attention to United States Patent Nos. 6,270,747 ("the '747 Patent"), issued August 7, 2001; 6,566,324, ("the '324 Patent"), issued May 20, 2003; and 6,551,989 ("the '989 Patent"), issued April 22, 2003 (all attached hereto). The '747 Patent claims are directed to methods for screening candidate agents for therapeutic potential in treating mucus hypersecretion in an airway comprising contacting an *in vitro* model of goblet cell differentiation with an EGF-R ligand. The '324 Patent claims are directed to methods of treating hypersecretion of mucus in lungs comprising administering a therapeutically effective amount of an EGF-R antagonist that binds the EGF-R. The '989 Patent claims are directed to pharmaceutical compositions for treatment of airway mucus hypersecretion comprising a therapeutically effective amount of an EGF-R antagonist that binds to an EGF-R.

Thus, it is well known in the prior art that the activity of EGF-R kinase is linked to diseases of the airways and lungs. Applicants submit that in light of the prior art and the teachings of

the present application, the claimed methods are fully enabled for treating or preventing diseases of the airways and lungs.

In addition, Applicants direct the Examiner's attention to the review article by Laird and Cherrington, Expert Opin. Invest. Drugs (2003) 12(1):51-64 (attached hereto) which describes numerous small molecule tyrosine kinase synthetic inhibitors including inhibitors of EGF-R tyrosine kinase (e.g., Iressa™; Astra Zeneca and Tarceva™; Genentech/Roche/OSI Pharmaceuticals) and HER2 (trastuzumab, Herceptin®; Genentech) for the treatment of human cancer. Moreover, Applicants submit that Iressa™ (genfitinib) was approved by the Food and Drug Administration on May 5, 2003 as a single agent treatment for patients with advanced non-small cell lung cancer. Thus, it is well known in the prior art that the activity of tyrosine kinases are linked to preventing or treating malignant tumors.

Applicants submit that the compounds of the present invention are not merely EGF-R kinase inhibitors, but also inhibit HER2 kinase activity. Applicants direct the Examiner's attention to the Declaration of Dr. Frank Himmelsbach Under 37 C.F.R. §1.132 ("the Himmelsbach Declaration"), submitted herewith. The Himmelsbach Declaration, at paragraph 5, describes experiments that demonstrate that the compounds of the invention inhibit both EGF-R kinase and HER2 tyrosine kinase.

Applicants submit that in light of the prior art and the teachings of the present application, the claimed methods are fully enabled for treating or preventing malignant tumors.

Applicants submit that in view of the amendments and remarks above, all of the rejections under 35 U.S.C. §112, first and second paragraphs have been overcome and must be withdrawn.

Double Patenting

Claims 17-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of co-pending U.S. Application No. 10/353,616 (US Publication No. 2003/0149062 A1). According to the Examiner, although the claims are not identical, they are not patentably distinct from each other because both applications claim a method for treating diseases of airways, lungs, and intestines (or

gastrointestinal tract) comprising administering an effective amount of a similar quinazoline compound.

Applicants emphatically disagree. Applicants direct the Examiner's attention to paragraphs 6 and 7 of the Himmelsbach Declaration. In order to demonstrate the unexpectedly improved inhibition of kinases of the tyrosine kinase family for the compounds of the present invention, a compound of the present invention (Example 1(10) of the present application) and a structurally similar compound (Example 3(30) of U.S. Patent Publication No. 2002/0169180) were screened in the EGF-R kinase and HER2 tyrosine kinase assays described on pages 18 to 19 of the above-identified application and in paragraph 5 above. The compounds differ only slightly in the R_b group. The R_b group of the compound of the invention is a dimethylamino group whereas the R_b group of the structurally related compound is a diethylamino group.

Thus, the compounds according to the invention of the above-identified patent application are much more active with regard to tyrosine kinase inhibition than those known in the cited prior art. Furthermore, this superiority was neither taught, suggested, nor deducible by the cited prior art. Moreover, such activity results would have been both surprising and unexpected to one of ordinary skill in the art of the subject matter of the invention. Accordingly, a consumer suffering from benign or malignant tumors or diseases of the airways and lungs would prefer to be treated with the more effective compounds of the present invention.

For the reasons above, Applicants submit that the methods of the present invention comprising administering the compounds of the present invention are patentably distinct from the methods of US Publication No. 2003/0149062 A1. Applicants respectfully submit that the rejection based on nonstatutory double patenting should be withdrawn.

CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. Applicants believe that each ground for rejection has been successfully overcome and that the application is in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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